REMARKS

The claims were amended to cancel claims to matter Applicants do not wish to prosecute at this time. Applicants reserve the right to prosecute claims to any canceled subject matter in this or future continuation applications. No new matter is introduced by these amendments.

If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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ART 34 AMDT

1. A method for identifying a compound that modulates protein translation, said method comprising:

a) providing a XIAP IRES reporter cistron;

b) exposing said XIAP IRES reporter cistron to a test compound;

c) determining the amount of translation from said XIAP IRES reporter cistron exposed to said compound, relative to the amount of translation from said XIAP IRES reporter cistron not exposed to said compound, wherein a relative increase in translation from said XIAP IRES reporter cistron exposed to said compound indicates a compound that increases XIAP IRES-dependent protein translation, and wherein a relative decrease in translation from said XIAP IRES reporter cistron exposed to said compound indicates a compound that decreases XIAP IRES-dependent protein translation.

2. The method of claim 1, wherein said XIAP IRES reporter cistron is exposed to a cell extract prior to being exposed to said test compound, said cell extract being capable of translating said XIAP IRES reporter cistron.

3. The method of claim 1, wherein said XIAP IRES reporter cistron is exposed to a cell extract after being exposed to said test compound, said cell extract being capable of translating said XIAP IRES reporter cistron.

4. The method of claim 1, further comprising providing an internal control reporter cistron, wherein:

a) the amount of translation from said XIAP IRES reporter cistron exposed to said compound is normalized relative to the amount of translation of said internal control reporter cistron exposed to said compound, and

b) the amount of translation from said XIAP IRES reporter cistron not exposed to said compound is normalized relative to the amount of translation of said internal control reporter cistron not exposed to said compound, and

c) the amount of normalized translation from said XIAP IRES reporter cistron exposed to said compound, relative to the amount of normalized translation from said XIAP IRES reporter cistron not exposed to said compound is determined, wherein a relative increase in normalized translation from said XIAP IRES reporter cistron exposed to said compound indicates a compound that increases XIAP IRES-dependent protein translation, and wherein a relative decrease in translation from said XIAP IRES reporter cistron exposed to said compound indicates a compound that decreases XIAP IRES-dependent protein translation.

5. The method of claim 1, wherein said XIAP IRES reporter cistron is within a cell, and wherein said cell is exposed to said test compound.

6. The method of claim 5, wherein said cell further comprises an internal control cistron, and wherein:

a) the amount of translation from said reporter cistron in said cell exposed to said compound is normalized relative to the amount of translation of said internal control cistron in said cell exposed to said compound, and

b) the amount of translation from said reporter cistron in said cell not exposed to said compound is normalized relative to the amount of translation of said internal control cistron in said cell not exposed to said compound, and

c) the amount of normalized translation from said reporter cistron in said cell exposed to said compound, relative to the amount of normalized translation from said reporter cistron in said cell not exposed to said compound is determined, wherein a relative increase in normalized translation from said reporter cistron in said cell exposed to said compound indicates a compound that increases XIAP IRES-dependent protein translation, and wherein a relative decrease in translation from said reporter cistron in said cell exposed to said compound indicates a compound that decreases XIAP IRES-dependent

protein translation.

7. A method for identifying a compound that modulates protein translation, said method comprising:

a) providing at least two reporter cistrons, wherein said reporter cistrons comprise an internal control reporter cistron and a XIAP IRES reporter cistron;

b) exposing said internal control reporter cistron and said XIAP IRES reporter cistron to said compound;

c) determining the amount of translation from said internal control reporter cistron and said XIAP IRES reporter cistron;

d) calculating the $\text{translation}_{\text{cisXI/cisIC}}$;

e) comparing $\text{translation}_{\text{cisXI/cisIC}}$ in a sample exposed to said compound to $\text{translation}_{\text{cisXI/cisIC}}$ in a sample not exposed to said compound, wherein an increase in $\text{translation}_{\text{cisXI/cisIC}}$ indicates a compound that increases XIAP IRES-dependent translation and wherein a decrease in $\text{translation}_{\text{cisXI/cisIC}}$ indicates a compound that decreases XIAP IRES-dependent translation.

8. The method of claim 7, wherein said reporter cistrons are exposed to a cell extract prior to being exposed to said test compound, said cell extract being capable of translating said XIAP IRES reporter cistron.

9. The method of claim 7, wherein said reporter cistrons are exposed to a cell extract after being exposed to said test compound, said cell extract being capable of translating said XIAP IRES reporter cistron.

10. The method of claim 7, wherein said reporter cistrons are within a cell, and wherein said cell is exposed to said test compound.

11. The method of claim 7, wherein said reporter cistrons comprise a single transcription unit.

12. The method of claim 7, wherein said internal control reporter cistron is located upstream from said XIAP IRES reporter cistron.

13. The method of claim 7, wherein said method is for identifying a compound that decreases XIAP IRES-dependent translation, wherein $translation_{cisXI/cisIC}$ in a cell exposed to said compound is decreased relative to $translation_{cisXI/cisIC}$ in a cell not exposed to said compound.

14. The method of claim 13, wherein said method is for identifying a compound useful for treating cancer.

15. The method of claim 7, wherein said method is for identifying a compound that increases XIAP IRES-dependent translation, wherein $translation_{cisXI/cisIC}$ in a cell exposed to said compound is increased relative to $translation_{cisXI/cisIC}$ in a cell not exposed to said compound.

16. The method of claim 7, further comprising a non-XIAP IRES reporter cistron, wherein said non-XIAP IRES reporter cistron is under the translational regulation of an IRES that is not a XIAP IRES.

17. The method of claim 16, wherein said IRES that is not a XIAP IRES is a VEGF IRES.

18. The method of claim 16, wherein said reporter cistrons comprise a single transcription unit and wherein said internal control reporter gene is located upstream from said XIAP IRES reporter cistron and said non-XIAP

IRES reporter cistron.

19. The method of claim 16, wherein said method further comprises:

f) calculating the $translation_{cisNX/cisIC}$;

g) comparing $translation_{cisNX/cisIC}$ in a sample exposed to said compound to $translation_{cisNX/cisIC}$ in a sample not exposed to said compound, wherein an increase in $translation_{cisNX/cisIC}$ indicates a compound that increases non-XIAP IRES-dependent translation and wherein a decrease in $translation_{cisNX/cisIC}$ indicates a compound that decreases non-XIAP IRES-dependent translation.

20. The method of claim 19, wherein said method is for identifying a compound for treating cancer, wherein:

a) $translation_{cisXI/cisIC}$ in a sample exposed to said compound is decreased relative to $translation_{cisXI/cisIC}$ in a cell not exposed to said compound, and

b) $translation_{cisNX/cisIC}$ in a sample exposed to said compound is decreased relative to $translation_{cisNX/cisIC}$ in a sample not exposed to said compound,

wherein said compound is useful for treating cancer.

21. The method of claim 19, wherein said method is for identifying a compound that inhibits apoptosis, wherein:

a) $translation_{cisXI/cisIC}$ in a sample exposed to said compound is increased relative to $translation_{cisXI/cisIC}$ in a sample not exposed to said compound, and

b) $translation_{cisNX/cisIC}$ in a sample exposed to said compound is increased relative to $translation_{cisNX/cisIC}$ in a sample not exposed to said compound,

wherein said compound is useful for inhibiting apoptosis in a cell in need thereof.

22. A method for decreasing a cell's resistance to apoptosis, said method comprising, introducing into said cell, an antisense nucleic acid having a sequence complementary to a XIAP IRES, wherein said antisense nucleic acid inhibits translation of XIAP in said cell.

23. The method of claim 22, wherein said cell is exposed to an apoptotic stimulus, wherein said apoptotic stimulus is gamma irradiation or a toxin.

24. A method for regulating the level of a protein in a cell, said method comprising introducing into said cell a nucleic acid, said nucleic acid comprising a XIAP IRES sequence.

25. The method of claim 24, wherein said nucleic acid further comprises a purified nucleic acid encoding a polypeptide, wherein the coding region for said polypeptide is under the translational regulation of a XIAP IRES, wherein the presence of said XIAP IRES sequence increases the level of cap-independent translation of said polypeptide.

26. The method of claim 25, wherein said polypeptide is selected from the group consisting of NAIP, TIAP, HIAP1, HIAP2, VEGF, BCL-2, BDNF, GDNF, PDGF-B, IGF-2, NGF, CTNF, NT-3, NT-4/5, EPO, insulin, TPO, p53, VHL, XAF, BAX, BCL-X_{LI}, TRADD, FADD, BAD, BCL-X_S, and caspases 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10.

27. The method of claim 22 or 25, wherein said cell is a cancer cell.

28. The method of claim 24, wherein said nucleic acid sequence further comprises a polypeptide coding sequence, wherein said polypeptide coding

sequence for said polypeptide is under the translational control of said XIAP IRES sequence.

29. The method of claim 28, wherein the presence of said XIAP IRES sequence increases the level of cap-independent translation of said protein.

30. The method of claim 28, wherein said cell is a cell at risk for undergoing apoptosis.

31. The method of claim 30, wherein said cell is at risk for undergoing apoptosis due to an autoimmune disease, a degenerative disease, or immunorejection.

32. The method of claim 30, wherein said cell is selected from the group consisting of: a neuron, a cardiomyocyte, a skeletal myoblast, a skeletal myofiber, a hair follicle cell, an ovarian follicle cell, a retinal photoreceptor cell, an oligodendrocyte, an astrocyte, and a pancreatic islet cell.

33. The method of claim 28, wherein said cell is undergoing a heat shock response.

34. The method of claim 28, wherein said cell is under environmental stress.

35. The method of claim 34, wherein said environmental stress is selected from the group consisting of: hypoxic stress, osmotic stress, oxidative stress, radiation-induced stress, or toxin-induced stress.

36. The method of claim 28, wherein said cell is growth-arrested.

37. The method of claim 28, wherein said cell is a cancer cell.

38. The method of claim 28, wherein said method is for inhibiting apoptosis in a cell in need thereof.

39. The method of claim 38, wherein said protein is selected from the group consisting of: XIAP, NAIP, TIAP, HIAP1, HIAP2, VEGF, BCL-2, BDNF, GDNF, PDGF-B, IGF-2, NGF, CTNF, NT-3, NT-4/5, EPO, insulin, TPO, and BCL-X_{L1}.

40. The method of claim 28, wherein said method is for reducing hypoxic stress in a tissue under hypoxic stress, wherein said protein is selected from the group consisting of: VEGF-1, VEGF-2, and b-FGF, wherein expression of said protein is sufficient to reduce hypoxic stress in said tissue.

41. The method of claim 40, wherein said tissue is cardiac tissue or brain tissue.

42. The method of claim 28, wherein said method is for stimulating apoptosis in a cell in need thereof.

43. The method of claim 42, wherein said protein is selected from the group consisting of: caspases 1-10, BAX, BAD, BCL-X_s, TRADD, FADD, XAF, VHL, and p53.

44. The method of claim 43, wherein said cell is a cancer cell.

45. A purified nucleic acid comprising a XIAP IRES, wherein, if nucleotides are present 5' or 3', said nucleic acid comprises at least one variant

nucleotide within a 500 nucleotide region 5' or 3' to said XIAP IRES, said variant nucleotide being a nucleotide that is not present at the position of said variant nucleotide in a naturally occurring XIAP gene or XIAP mRNA, relative to the position of said XIAP IRES, wherein said XIAP IRES increases cap-independent translation of a cistron when located upstream from said cistron within a messenger RNA molecule.

46. The nucleic acid of claim 45, wherein said XIAP IRES increases stress-induced cap-independent translation.

47. A purified nucleic acid comprising a XIAP IRES, wherein, if nucleotides are present 5' or 3' to said XIAP IRES, said nucleic acid comprises at least one variant nucleotide within a 500 nucleotide region 5' or 3' to said XIAP IRES, said variant nucleotide being a nucleotide that is not present at the position of said variant nucleotide in a naturally occurring XIAP gene or XIAP mRNA, relative to the position of said XIAP IRES, wherein said XIAP IRES increases cap-independent translation of a cistron when located upstream from said cistron within a messenger RNA molecule.

48. A purified nucleic acid comprising a XIAP IRES, said XIAP IRES being 5' to a coding sequence that encodes a polypeptide other than a human or murine XIAP.

49. A purified nucleic acid comprising a mammalian XIAP IRES, said IRES being 5' to a coding sequence that encodes a polypeptide other than mammalian XIAP.

50. A purified nucleic acid that hybridizes to a probe comprising at least ten nucleic acids from the XIAP IRES, said nucleic acid not including the

full XIAP cDNA sequence.

51. A purified nucleic acid comprising a mammalian XIAP IRES, wherein, if nucleotides are present 5' or 3' to said XIAP IRES, said XIAP IRES has a nucleotide sequence substantially identical to a nucleotide sequence set forth in SEQ ID NOs: 19-30, wherein said nucleic acid comprises at least one variant nucleotide within a 500 nucleotide region 5' or 3' to said XIAP IRES, said variant nucleotide being a nucleotide that is not present at the position of said variant nucleotide in a naturally occurring XIAP mRNA, relative to the position of said XIAP IRES.

52. A purified nucleic acid comprising a mammalian XIAP IRES, wherein said XIAP IRES has a nucleotide sequence substantially identical to a nucleotide sequence set forth in SEQ ID NOs 19-30, wherein said nucleic acid comprises at least one variant nucleotide within a 500 nucleotide region 5' or 3' to said XIAP IRES, said variant nucleotide being a nucleotide that is not present at the position of said variant nucleotide in a naturally occurring XIAP mRNA, relative to the position of said XIAP IRES.

53. A purified nucleic acid comprising a nucleotide sequence complementary to at least 14 nucleotides of a nucleotide sequence of a nucleic acid selected from the group consisting of:

a nucleic acid comprising a XIAP IRES, wherein, if nucleotides are present 5' or 3' to said XIAP IRES, said nucleic acid comprises at least one variant nucleotide within a 500 nucleotide region 5' or 3' to said XIAP IRES, said variant nucleotide being a nucleotide that is not present at the position of said variant nucleotide in a naturally occurring XIAP gene or XIAP mRNA, relative to the position of said XIAP IRES, wherein said XIAP IRES increases cap-independent translation of a cistron when located upstream from said

cistron within a messenger RNA molecule;

a nucleic acid comprising a mammalian XIAP IRES, said IRES being 5' to a coding sequence that encodes a polypeptide other than mammalian XIAP; and

a nucleic acid comprising a mammalian XIAP IRES, wherein said XIAP IRES has a nucleotide sequence substantially identical to a nucleotide sequence set forth in SEQ ID NOs: 19-30, wherein said nucleic acid comprises at least one variant nucleotide within a 500 nucleotide region 5' or 3' to said XIAP IRES, said variant nucleotide being a nucleotide that is not present at the position of said variant nucleotide in a naturally occurring XIAP mRNA, relative to the position of said XIAP IRES.

54. The nucleic acid of claim 47, 49, 52, or 53, wherein said nucleic acid is contained within an expression vector and wherein said expression vector encodes a transcription unit comprising a XIAP IRES and a coding sequence for a polypeptide.

55. The nucleic acid of claim 54, wherein said coding sequence encodes a polypeptide that is not a XIAP polypeptide.

56. The nucleic acid of claim 54, wherein said expression vector is a gene therapy vector.

57. A vector containing nucleic acid comprising a XIAP IRES, wherein said nucleic acid comprising said XIAP IRES is 5' to nucleic acid encoding a polypeptide, wherein said polypeptide is selected from the group consisting of: XIAP, NAIP, TIAP, HIAP1, HIAP2, VEGF, BCL-2, BDNF, GDNF, PDGF-B, IGF-2, NGF, CTNF, NT-3, NT-4/5, EPO, insulin, TPO, p53, VHL, XAF, BAX, BCL-X_{L1}, BAD, BCL-X_S, and caspases 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10.

58. The vector of claim 57, wherein said vector further comprises a promoter, wherein said promoter is a tissue-specific promoter.

59. A method for detecting a compound that modulates XIAP IRES-dependent translation, said method comprising:

(a) providing a sample comprising La autoantigen;

(b) exposing said sample to a test compound;

(c) contacting said La autoantigen with a XIAP IRES or an endogenous XIAP IRES; and

(d) measuring the amount of binding of La autoantigen to said XIAP IRES or said endogenous XIAP IRES, wherein a decrease in said binding indicates a compound that decreases XIAP IRES-dependent translation, and wherein an increase in said binding indicates a compound that increases XIAP IRES-dependent translation.

60. The method of claim 59, wherein said La autoantigen is contacted with said XIAP IRES or said endogenous XIAP IRES prior to exposing said sample to said test compound.

61. The method of claim 59, wherein said La autoantigen is contacted with said XIAP IRES or said endogenous XIAP IRES after exposing said sample to said test compound.

62. A method for decreasing a cell's resistance to apoptosis, said method comprising exposing said cell to a compound that decreases the binding of La autoantigen to an endogenous XIAP IRES, wherein a decrease in said binding is sufficient to decrease translation of XIAP in said cell.

63. The method of claim 62, wherein said cell is a tumor cell or is at

risk for becoming a tumor cell.

64. A method for increasing a cell's resistance to apoptosis, said method comprising exposing said cell to a compound that increases the binding of La autoantigen to an endogenous XIAP IRES, wherein an increase in said binding is sufficient to increase translation of XIAP in said cell.

65. The method of claim 64, wherein said cell has an increased risk for undergoing apoptosis.

66. The method of claim 25, wherein said polypeptide is a polypeptide that stimulates apoptosis.

67. The method of claim 25, wherein said polypeptide is a polypeptide that inhibits apoptosis, and wherein if said polypeptide is XIAP, said nucleic acid comprises at least one variant nucleotide within a 500 nucleotide region 5' or 3' to said XIAP IRES, said variant nucleotide being a nucleotide that is not present at the position of said variant nucleotide in a naturally occurring XIAP mRNA, relative to the position of said XIAP IRES.